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3D Printed Reactionware for Synthetic Electrochemistry with Hydrogen Fluoride Reagents

David M. Heard[+], Sayad Doobary[+], and Alastair J. J. Lennox*[a]

Electrochemical fluorination reactions of organic compounds frequently employ hydrogen fluoride reagents that are corrosive. The corrosive nature of these reagents necessitates either the construction or purchase of cells that are stable to hydrogen fluoride, which require high-cost materials, machining time and expertise. Herein, we offer an alternative solution using 3D printing, which is an inexpensive and rapid manufacturing technique. We have designed, printed and shared four different cell types in polypropylene and tested them in an electrochemical alkene difluorination reaction in the presence of triethylamine·3HF and pyridinium poly·(HF).

The combination of electrochemistry and hydrogen fluoride-based reagents is an effective general approach to oxidatively installing fluorine into organic compounds, Figure 1A.[1–7] Fluorinated compounds are of broad interest to the pharmaceutical and agrochemical industries due to their unique influence on the bioactivity of a molecule.[8–13] Anodic oxidation provides a tuneable and selective mode of oxidation that can be readily varied to match the potential of the substrate or mediator. Hydrogen fluoride (HF) is, in general, inexpensive, as it is readily formed directly from natural fluorspar upon heating in sulfuric acid.[14] While aqueous and anhydrous forms of HF have significant and prohibitive safety concerns associated with them,[15] commercially available organic sources of HF, such as triethylamine·3HF and pyridinium poly(HF) ('Olah's reagent', which is a mixture of 70% HF in pyridine), are highly versatile fluoride reagents and frequently employed for electrochemical fluorination reactions. The potential windows of these two reagents depend on the ratio of HF to organic base,[16] but are generally tolerant of the oxidative potentials required, while the protons are readily reduced to hydrogen gas on the counter electrode. These organic basic HF sources are readily soluble in organic solvent, and these solutions are sufficiently conductive that supporting electrolyte is often not required due to their (partial) ionic nature. Thus, the combination of anodic oxidation and hydrogen fluoride has been used for the fluorination of alkenes,[7,17–25] alkynes,[18] aromatic rings,[26–29] esters,[30–32] ketones[16,33] and thioketals,[34–38] among others, Figure 1A. *Warning: Extreme care should always still be used in handling these materials; handle only in a fume hood, wear safety goggles or a face shield, and wear appropriate impermeable clothing.*

Although $NEt_3 \cdot 3HF$[39] is much less corrosive than pyridinium poly(HF),[40] the use of either reagent, but especially the latter, in regular glassware is not recommended. Not only does the glassware etch and weaken, but silicon and boron contaminants leach into the solution, which can interfere with the chemistry.[41] Most commercially available electrochemical cells are produced using regular pyrex-based glass, and the HF-compatible polymer- based electrochemical cells are much rarer and more expensive (see SI for details). Therefore, it is most common to construct HF-compatible electrochemical cells in-house, and most commonly from PTFE. However, the in-house machining tools and equipment required, the high costs of materials, and the potentially long lead times associated with their fabrication can be prohibitive.

Considering the rise in 3D printing technology and the scale of its adoption, we sought a solution to HF compatible electrochemical reactors using this manufacturing technique.

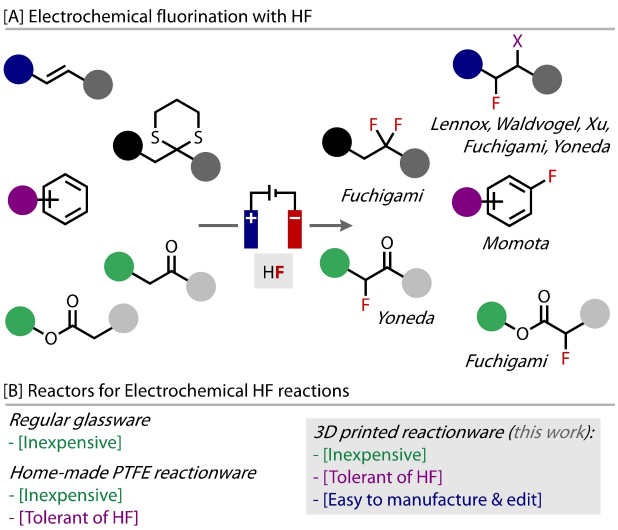

Figure 1. [A] Electrochemical oxidation and hydrogen fluoride reagents have combined to introduce fluoride to organic compounds. [B]: reactor materials and their associated characteristics.

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3D printing, or additive manufacturing, is a rapidly maturing technology that has progressed from an engineering curiosity to become a viable, cost-effective manufacturing or prototyping technique with applications in several fields of research,[42–47] including chemical synthesis,[48–56] analytics,[57–61] and, albeit to a lesser extent, synthetic electrochemistry.[49,62–67] As the object is built up layer by layer in a computer-controlled process, high resolution objects can be rapidly manufactured without the operator having to be familiar with the range of machining instruments and techniques normally employed. In combination with Computer Aided Design (CAD), unusual or unconventional shapes and structures can be created, including internal structures that are not easily produced by other manufacturing approaches.[68] The cost of 3D printing has also decreased over the last decade, with an increasing number of inexpensive printers on the market, and free CAD software packages and online 3D printing services available (see SI for more details).[69] Herein, we demonstrate 3D printing as a facile and cost-effective technique to create electrochemical cells capable of handling the harsh reaction conditions inherent in the use of hydrogen fluoride in organic synthesis, Figure 1B. We also share the files needed to print four reactors with different configurations, scales, and for use with different potentiostat-types.

Results and Discussion

We recently reported conditions for an alkene difluorination reaction that combined electrochemical oxidation with a mixture of $NEt_3 \cdot 3HF$ and pyridinium poly(HF) in CH_2Cl_2/hexafluoro isopropanol (HFIP) with 4-iodotoluene as mediator, Figure 2.[17] In this transformation, an undivided cell can be used for more oxidatively stable substrates, but a divided cell is required, in an ex-cell approach, for oxidatively sensitive substrates. The reaction was also demonstrated on a larger scale and with the commercially available ElectraSyn 2.0 set-up. With this variety of reactor-types demonstrated and the corrosive conditions used, we reasoned this was a good transformation to showcase 3D printed electrochemical reactors for use with hydrogen fluoride reagents.

Autodesk Fusion360 CAD package was used to design four different electrochemical reactors, including an undivided cell, a cell compatible with the ElectraSyn, a divided cell for small scale and a divided cell for larger scale. The cells were printed using the Fused Deposition Modelling (FDM) technique.[70] In this method, a continuous filament of feedstock polymer passes through a heated chamber, which melts it and allows it to be extruded through a small nozzle where it adheres to the growing object.[62] As it is one of the most ubiquitous 3D printing techniques several different polymer filaments are available, with polylactic acid (PLA) and acrylonitrile butadiene styrene (ABS) the most commonly used materials. For synthetic chemistry reactionware, polypropylene (PP) has emerged as the material of choice due to its greater chemical resistance,[71] and because the inexpensive filament can be printed on most typical FDM printers. In particular, PP has good resistance to HF and most common organic solvents,[72] making it well suited to the design of electrochemical cells. Thus, all four reactors were printed using PP filament on a FDM printer. The glass print bed was layered with PP tape to ensure good adherence of the extruded PP to the surface during the printing process. In all cases, the reactors were printed with 100% infill to reduce the risk of leaks.

Undivided Cell

For alkene substrates with oxidation potential greater than 1.8 V (vs Fc/Fc^+), an undivided cell can be used for the vicinal difluorination. The reported cell for reaction of **1** to **2** was constructed from a commercially available HDPE vial and an up-turned septum that served as a lid to secure the electrode wires. Using this set-up, a ^{19}F NMR yield of 90% was achieved, Scheme 1. We have now repeated this reaction using a glass (type III soda lime glass) vial instead of the HDPE vial, and a dramatic drop in yield to 17% was observed. This remarkable difference in yield on simply switching the cell material further emphasises the requirement to ensure an HF stable material is used for these reaction systems. The reaction of hydrogen fluoride with the silica in the glass vial presumably depletes the available HF that is necessary for successful reaction, or the generation of SiF_4[41] may be detrimental to reaction progress.

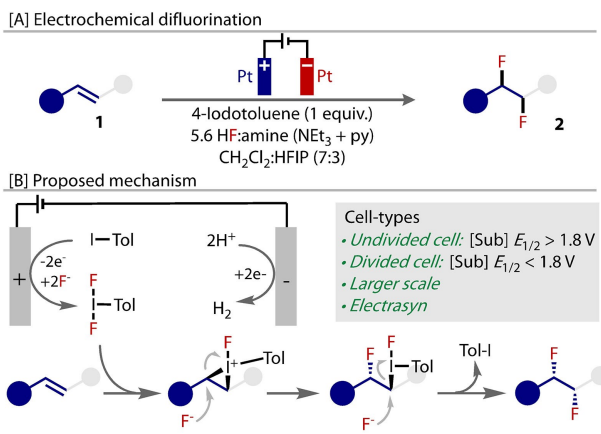
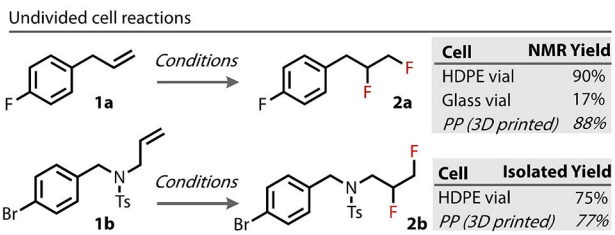


Figure 2. [A] Optimised conditions for the electrochemical difluorination of alkenes, [B] mechanism of the reaction, mediated by tolyl-iodide.



Scheme 1. A comparison of cell materials for the difluorination of **1a** and **1b** to **2a** and **2b**, respectively.

A 3D printed PP cell was designed with an internal cylindrical volume of 25 mL, which is capable of converting up to 6 mmol of substrate **1** at a concentration of 300 mM, Figure 3 A threaded lid was designed and printed that combines with an O-ring to compress onto the reactor body and seal it from the outside environment, reducing solvent evaporation and facilitating the creation of inert atmosphere when combined with an N_2 line. The lid contains holes for electrodes and/or a septum to be inserted. The 3D printed lids facilitate a consistent electrode separation distance and provides more accurate control of the electrode submersion, both of which are important parameters for reproducible and controllable synthetic electrochemical reactions. When the difluorination of alkenes **1a** and **1b** was conducted in this PP cell, the NMR and isolated yields were consistent with those conducted in the reported HDPE cell, Scheme 1.

To investigate the reusability of the 3D printed PP reaction vessels, we repeated the reaction of **1b** to **2b** 5 times in the undivided cell, Figure 4. During each reaction, no leaks were observed, and the yield of **2b** from **1b** remained consistent after each successive run, signifying the reusability of these vessels.

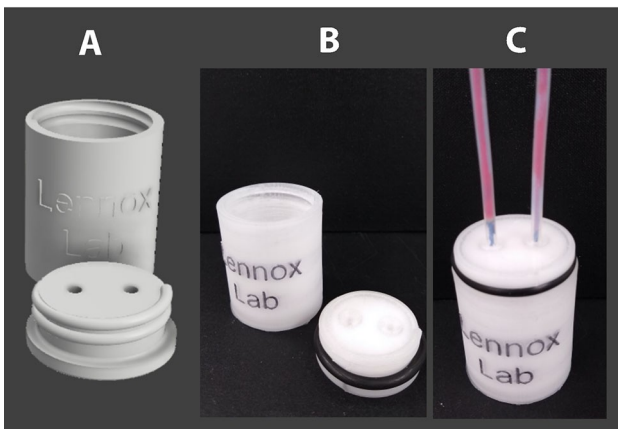


Figure 3. A) CAD drawing; B) and C) 3D printed undivided cell

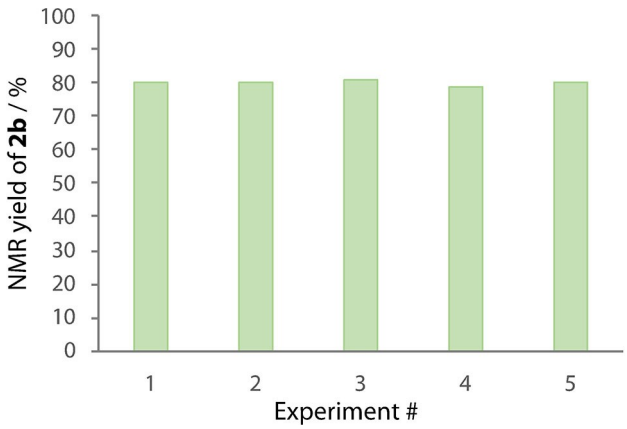


Figure 4. Repeat reactions of **1b** to **2b** in the same 3D printed undivided cell.

ElectraSyn Vial

A separate undivided cell was designed to be compatible with the ElectraSyn 2.0,[73] in order to expand the system's compatibility with electrochemistry and HF, while maintaining the ability to use commercially available lids and electrodes, Figure 5. The cell contains a threaded body that screws into the head of the unit. When testing the reaction of **1a** to **2a** on the ElectraSyn in the 3D printed reactor, a comparable yield was attained with a bespoke vial made of PTFE, Scheme 2. With many 3D-printing services available online (see SI for details), access to these vials to connect to this commercially available and standardised equipment is straightforward and inexpensive, and may even offer a cost effective alternative to the regular vials for other transformations and conditions

Divided Cell

For alkene substrates containing more electron rich moieties with oxidation potentials <1.8 V (vs Fc/Fc^+), a divided cell must be used in an ex-cell approach. Hence, 4-iodotoluene is oxidised at the anode to form the *p*-tolyl difluoro λ^3 iodane (*p*-TolIF$_2$), after which the alkene is added. A divided cell is necessary to ensure longer term stability of the generated hypervalent iodine reagent. The reported cell for this approach was fabricated from PTFE and inspired by an existing design reported by Waldvogel.[74] In this reaction set-up, an 83% isolated yield of **2c** was attained from **1c**, Scheme 3. As a subtractive manufacturing technique was used for this cell, the design was adapted for our 3D printed divided cell in order to reduce the quantity of material required for printing. The cell design allows either a glass frit or membrane to be secured

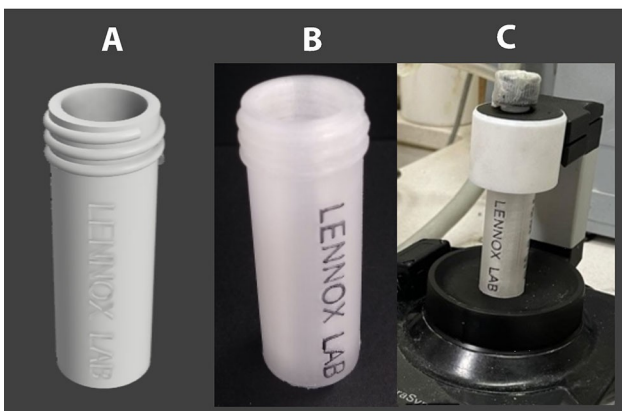
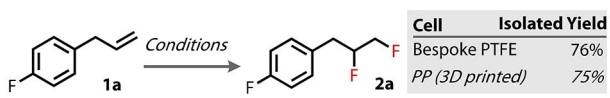


Figure 5. Design and printing process of the Electrasyn-compatible reactor. A) CAD drawing, B) Completed printed reactor and C) reactor in use



Cell	Isolated Yield
Bespoke PTFE	76%
PP (3D printed)	*75%*

Scheme 2. a comparison of cells for the difluorination of **1a** to **2a**.

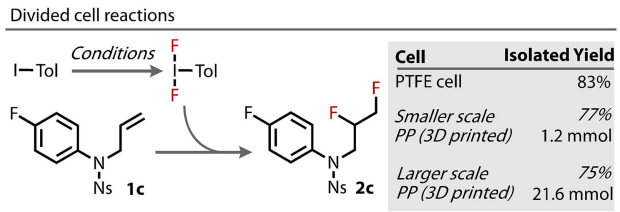
between the compartments, which is sealed with an EPDM O-ring (ID = 18.7 mm) (in our case, a nafion membrane was used). Both push-fit and threaded lids were produced to facilitate ease of use. Two sizes of divided cell were designed and printed for two different scales. Thus, a cell with 10 mL internal volume for both the anodic and cathodic compartments was produced, which we tested with a 1.2 mmol scale reaction that gave a comparable 77% isolated yield of **2c**.

A divided cell with 50 mL compartments was also designed, Figure 6. The lids for this larger scale reactor were designed to readily accommodate multiple electrodes. The holes were accurately and closely positioned in order for 3 electrodes to be connected in parallel to effectively increase the surface area of the counter electrode. The larger surface area enables a more rapid electrolysis at the same current density, which was found to be necessary for this system due to the light, temperature and air sensitivity of *p*-TolIF$_2$. An EPDM sponge gasket was applied to ensure a tight seal between the two halves in order to avoid leaking. A 21.6 mmol scale (deca-gram) reaction was tested in the reactor, and an isolated yield of 75% for **2c** was achieved, Scheme 3.

Conclusion

In summary, we have designed, printed and tested four reactor systems that are suitable for synthetic electrochemistry with hydrogen fluoride reagents. The PP is resistant to HF consumption and therefore all yields observed were directly comparable to other HF resistant materials, such as HDPE or PTFE. By sharing the .stl files, these reactors should be readily accessible for others to use with electrochemistry and hydrogen fluoride reagents.

Supporting Information: Synthetic procedures, characterisation data and cell assembly instructions are given in the Supporting Information. Data files required for reactor 3D printing are available at the University of Bristol data repository, data.bris, at https://doi.org/10.5523/bris.2yj6li188q2911zo0rla600gbf.



Scheme 3. A comparison of cell materials for the reaction of **1c** and **2c**.

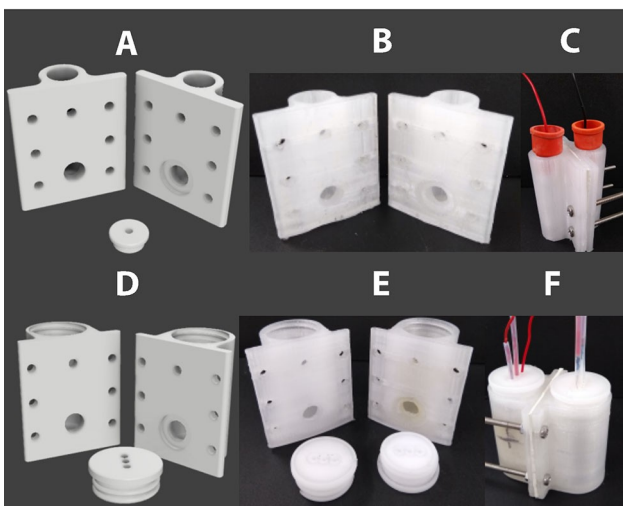


Figure 6. CAD drawings and 3D printed divided cells, for smaller (upper) and larger (lower) scales.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: 3D printing · CAD · fluorination · synthetic electrochemistry · alkenes

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